Austin Journal of Clinical Neurology

Open Access

Austin Publishing Group

Editorial

Current Understanding of Immunopathogenesis of Parkinson's Disease

Tatsuro Mutoh*

Department of Neurology and Neuroscience, Fujita Health University School of Medicine, Japan

***Corresponding author:** Tatsuro Mutoh, Department of Neurology and Neuroscience, Fujita Health University School of Medicine, 1-98 Dengakugakubo, Kutsukake-cho, Toyoake, Aichi 470-1192, Japan

Received: December 12, 2016; **Accepted:** December 27, 2016; **Published:** December 30, 2016

Editorial

Parkinson's Disease (PD) is a common neurodegenerative disease with second most common incidence world-widely. The underlying cause of PD remains yet to be elucidated, the recent study has revealed gene mutations encoding the lysosomal acid hydrolase, glucocerebrosidase (GBA1[OMIM 606463]) is a strong genetic risk factor for idiopathic PD [1], although another non-lysosomal neutral glucocerebrosidase, GBA2 is present. GBA 1, but not GBA2 activity is deficient in Gaucher's disease, and it has been noticed that in patients with Gaucher's disease, PD is more frequently encountered than normal populations [2]. Some hypothesis is pointed as to the lysosomal impairment contributes to an altered aggregation and degradation of α-synuclein which is thought to be a main neuro pathological protein for PD [3]. Intriguingly, very recent report indicated α-synuclein monomer can interact with mitochondrial ATP synthase and promote its enzymatic activity [4]. Then, although at present, the molecular mechanisms for α-synuclein aggregation remains to be elucidated, an interesting observation by Usuki et al. suggested that acylated steryl glucoside promote the aggregation of α-synuclein and therefore enhances its neurotoxicity [5]. Intriguingly, a previous study has suggested that heat shock stress up regulates the contents of steryl glucoside in human fibroblasts [6] and it is reported to be produced by the action of GBA2 activity.

Parkinson's disease and dysfunction of immune system

Recent investigations have revealed a significant contribution of the immune system in the etiology of PD. Several investigators have disclosed that microglial activation, an increase in the expression of inflammatory genes, local inflammation, and infiltration of immune cells in the brain of PD patients were observed [7]. Moreover, a recent report has shown that DA neurons express MHC class I molecules at their surface in the presence of activated microglia and inflammation [8]. Furthermore, PINK1 and Parkin, PD-related proteins are now identified as the strong suppressors of antigen presentation from the mitochondria in immune cells [9], which imply that PD patients exhibiting mutations of these proteins result in the increased antigen presentation from mitochondria and therefore exacerbated neuro-inflammation.

As for MHC class II molecules, an increases in MHC II positive cells have long been recognized in human postmortem tissue from PD patients [10] and 1-methyl-4-phenyl-1,2,3,6-tetrahydropiridinum (MPTP)-induced Parkinson model mice brain [11]. MHC class II molecules are required for the recruitment of $CD4^+$ T-cells in the brain. In fact, mice null for $CD4^+$ T-cells are protected from MPTP toxicity [12].

MHC molecules and T-cell activation

Previous studies have implicated that PD pathogenesis is associated with neuroinflammation, where the maturation of dendritic cells (DCs) and their migration to the respective sites in brain occur [13]. DCs can trigger an autoimmune response by transferring brain antigens into the cervical lymph nodes and presenting them to T- and B-cells. T-Cell activation of dendritic cells can occur by glycolipids, but presentation of the glycolipids on MHC class II molecules have been thought to be impossible [14]. Then, the question of how can IgG autoantibodies be generated against glycolipids comes out, because these glycolipids are not presented on MHC II molecules that stimulate helper T cells. Although the detailed molecular mechanism for the production of autoantibody against glycolipids remains unknown, autoantibody against glycolipids such as GM1 ganglioside has been detected in PD patents [15].

On the other hand, natural killer T (NKT) cells can recognize glycolipids. The prototype glycolipid antigen for NKT cells has been known as α-galactosylceramide and it helps to produce glycolipid-specific autoantibody without anti-specific $CD4^+$ T-helper cells [16]. The subsequent study clearly indicated the other neutral glycolipids such as glucosylceramide and lactosylceramide can be recognized by NKT cells [15]. Alternatively, soluble factors present in the supernatant of the glycolipids activated DCs may directly be able to circumvent both T cell and NKT cell help [14]. In any case, we need further vigorous investigations on these issues for the complete understanding of the pathogenesis of this disorder.

During the preparation of the manuscript, very important and intriguing paper came out to report that microbiota in the gut affect α-synuclein aggregation and motor performance in mice by way of the microglia-dependent pathway. Moreover, they identified one of the gut-brain signaling molecules as short chain fatty acids, which can cross the brain-blood-barrier and therefore can activate microglia within brain [17].

Thus, these accumulating evidences shed a light on the new avenue for our future investigations. This new trend of the research will possibly give us new therapeutic methods for PD patients.

References

1. Sardi SP, Singh P, Cheng SH, Shihabuddin LS, Schlossmacher MG. Mutant GBA1 expression and synucleinopathy risk: first insights from cellular and mouse models. Neurodegener Dis. 2012; 10: 195-202.

2. Bultron G, Kacena K, Pearson D, Boxer M, Yang R, Sathe S, et al. The risk

Citation: Mutoh T. Current Understanding of Immunopathogenesis of Parkinson's Disease. Austin J Clin Neurol 2016; 3(3): 1097.

of Parkinson's disease in type 1 Gaucher disease. J Inherit Metab Dis. 2010; 33: 167-173.

3. Mazzulli JR, Xu YH, Sun Y, Knight AL, McLean PJ, Caldwell GA, et al. Gaucher disease glucocerebrosidase and α-synuclein form a bidirectional pathogenic loop in synucleinopathies. Cell. 2011; 146: 37-52.

4. Ludtmann MH, Angelova PR, Ninkina NN, Gandhi S, Buchman VL, Abramov AY. Monomeric Alpha-Synuclein Exerts a Physiological Role on Brain ATP Synthase. J Neurosci. 2016; 36: 10510-10521.

5. Usuki S, Kamitani T, Matsuo Y, Yu RK. Pathobiochemical effect of acylated steryl-β-glucoside on aggregation and cytotoxicity of α-synuclein. Neurochem Res. 2012; 37: 1261-1266.

6. Kunimoto S, Kobayashi T, Kobayashi S, Murakami-Murofushi K. Expression of cholesteryl glucoside by heat shock in human fibroblasts. Cell Stress Chaperones. 2000; 5: 3-7.

7. Kannarkat GT, Boss JM, Tansey MG. The role of innate and adaptive immunity in Parkinson's disease. J Parkinsons Dis. 2013; 3: 493-514.

8. Cebrián C, Zucca FA, Mauri P, Steinbeck JA, Studer L, Scherzer CR, et al. MHC-I expression renders catecholaminergic neurons susceptible to T-cell-mediated degeneration. Nat Commun. 2014; 5: 3633.

9. Matheoud D, Sugiura A, Bellemare-Pelletier A, Laplante A, Rondeau C, Chemali M, et al. Parkinson's disease-related proteins PINK1 and Parkin repress mitochondrial antigen presentation. Cell. 2016; 166: 314-327.

10. McGeer PL, Itagaki S, Boyes BE, McGeer EG. Reactive microglia are positive for HLA-DR in the substantia nigra of Parkinson's and Alzheimer's disease brains. Neurology. 1988; 38: 1285-1291.

11. Martin HL, Santoro M, Mustafa S, Riedel G, Forrester JV, Teismann P. Evidence for a role of adaptive immune response in the disease pathogenesis of the MPTP mouse model of Parkinson's disease. Glia. 2016; 64: 386-395.

12. Brochard V, Combadiere B, Prigent A, Laouar Y, Perrin A, Beray-Berthat V, et al. Infiltration of CD41 lymphocytes into the brain contributes to neurodegeneration in a mouse model of Parkinson disease. J Clin Invest. 2009; 119: 182-192.

13. Kuijf ML, Samsom JN, van Rijs W, Bax M, Huizinga R, Heikema AP, et al. TLR4-mediated sensing of Campylobacter jejuni by dendritic cells is determined by sialylation. J Immunol. 2010; 185: 748-755.

14. Zappia M, Crescibene L, Bosco D, Arabia G, Nicoletti G, Bagalà A, et al. Anti-GM1 ganglioside antibodies in Parkinson's disease. Acta Neurol Scand. 2002; 106: 54-57.

15. Lang GA, Exley MA, Lang ML. The CD1d-binding glycolipid alpha-galactosylceramide enhances humoral immunity to T-dependent and T-independent antigen in a CD1d-dependent manner. Immunology. 2006; 119: 116-125.

16. Lalazar G, Ben Ya'acov A, Eliakim-Raz N, Livovsky DM, Pappo O, Preston S, et al. Beta-glycosphingolipids-mediated lipid raft alteration is associated with redistribution of NKT cells and increased intrahepatic CD8+ T lymphocyte trapping. J Lipid Res. 2008; 49: 1884-1893.

17. Sampson TR, Debelius JW, Thron T, Janssen S, Shastri GG, Ilhan ZE, et al. Gut Microbiota Regulate Motor Deficits and Neuroinflammation in a Model of Parkinson's Disease. Cell. 2016; 167: 1469-1480.

Austin J Clin Neurol - Volume 3 Issue 3 - 2016
ISSN : 2381-9154 | www.austinpublishinggroup.com

Citation: Mutoh T. Current Understanding of Immunopathogenesis of Parkinson's Disease. Austin J Clin Neurol 2016; 3(3): 1097.